General

Guideline Title

Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Technology appraisal guidance; no. 321).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Unresectable or metastatic BRAF V600 mutation-positive melanoma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Dermatology

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

Target Population

Adults with unresectable or metastatic BRAF V600 mutation-positive melanoma

Interventions and Practices Considered

Dabrafenib

Major Outcomes Considered

- Clinical effectiveness
  - Progression-free survival
  - Overall survival
  - Overall response rate
  - Duration of response
  - Health-related quality of life
  - Adverse effects of treatment
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Methods of Review(s)

Searches

Bibliographic databases including MEDLINE (1980 onwards and In process and other non-indexed citations), EMBASE (1980 onwards) and the Cochrane Library (1980 onwards) were searched on 22 October 2012. These searches were updated in October 2013 to identify additional published studies of relevance to the submission. No strategies for identifying ongoing studies are provided in the manufacturer's submission (MS). For all databases, a combination of free text and index terms were appropriately used.

Inclusion Criteria

The inclusion and exclusion criteria used in the original systematic review (October 2012) are presented in detail in the MS (Table 3). The criteria for the updated review are summarised in the table below. In addition to the interventions and comparators specified by NICE, it is noted that trametinib, ipilimumab and fotemustine were also included. It is stated that these interventions were identified from clinical practice or from ongoing clinical trials for the treatment of metastatic melanoma. The ERG notes that as of October 2013, both dabrafenib monotherapy and dabrafenib + trametinib (dual therapy) were included in the NICE appraisal process.

Table. Eligibility Criteria Used for Manufacturer's Updated Systematic Review (October 2013)

Parameter	Included	Excluded
Population	Adults with advanced or metastatic melanoma	• Studies of patients with other types of skin cancer were not included. • Studies with no subgroup data for the disease were not included, as these studies could introduce heterogeneity into the review. • Studies which enrolled a mixed population of stage I, II, III, and IV melanoma were only included if there was a subgroup analysis on the stage III and/or IV patient population.
Interventions	Dabrafenib; trametinib; vemurafenib; dacarbazine	Other interventions
Comparators	Vemurafenib; dacarbazine	Other comparators
Outcomes	Efficacy: OS; PFS; ORR: CR + PR; proportion of patients with stable disease and progressive disease; TTR, DoR; HRQoL Safety: Incidence and severity of all AEs; incidence and severity of specific AEs; withdrawals due to AEs; withdrawals due to death; SAEs	Other outcomes
Study design	RCTs	All other types of studies, reviews, letters and commentaries
Language	English	Not English

AE, adverse event; CR, complete response; DoR, duration of response; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; RCT, randomised controlled trial; SAE, serious adverse event; TTR, time to treatment response

Summary of the ERG's Critique of Submitted Clinical Effectiveness Evidence

The ERG is satisfied with the search strategy employed by the manufacturer to identify clinical effectiveness studies. It does not believe there are additional studies relevant to the decision problem which have not been identified by the manufacturer.

Cost-effectiveness

Overview of Manufacturer's Cost-effectiveness Literature Review

Objective of the Manufacturer's Cost-effectiveness Literature Review

The manufacturer's search was designed to capture economic literature which focussed on treatments for metastatic melanoma. The initial searches were conducted on 10 April 2012 and were updated on the 24 and 25 October 2013. The databases were searched from start of database (1960) to 24/25 October 2013.

The following data sources were used to retrieve economic and quality of life evidence:

- Medline (Embase.com; http://www.embase.com/)
- EMBASE (Embase.com; http://www.embase.com/)
- MEDLINE In-process (PubMed [in-process citations]; http://www.ncbi.nlm.nih.gov/sites/entrez)
- Cochrane (National Health Service Economic Evaluation Database [NHS EED]) (Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html)
- Cochrane (CENTRAL and Method Studies) (Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html)
- EconLIT (AEAweb.org interface)

The manufacturer states that a search of the Centre for Reviews and Dissemination (CRD) database was also undertaken to identify relevant technology appraisals.

Inclusion and Exclusion Criteria Used in Study Selection

Table. Economic Evaluation Search Inclusion and Exclusion Criteria

Parameter	Selection Criteria
Inclusion Criteria	
Population	Adults (males and females) of any age or race with unresectable advanced or metastatic or malignant melanoma (Stage IIIc or IV)
Study type and design	Cost studies/surveys/analyses; database studies collecting cost data; resource surveys; cost effectiveness analyses; cost utility analyses; cost benefit analyses; cost minimisation analyses; budget impact models; cost consequences studies
Intervention	All pharmacological treatments; all treatments including adjuvant therapy; surgery, radiotherapy or isolated limb perfusion; any other treatment
Countries	All
Language restriction	English only
Publication timeframe	No date restriction for database searches; Year 2009 to 2011 for conference proceedings
Exclusion Criteria	
Subgroup analyses	Subgroup data for the disease of interest, adult population, disease stage

Parameter	Selection Criteria
Language	Languages other than English

Summary of the ERG's Critique of Cost-effectiveness Evidence Submitted

The ERG is satisfied with the search strategy employed by the manufacturer to identify cost effectiveness studies, and is reasonably confident that no other relevant published articles exist. In addition, the ERG agrees with the manufacturer's view that there is insufficient evidence to facilitate the development of an economic case for previously treated (second-line) patients.

Number of Source Documents

Clinical Effectiveness

One study (BREAK-3) was the only identified trial that examined the effects of dabrafenib; therefore, it was considered to be the key trial of interest. Supporting evidence was also provided from four other studies, none of which were used in quantitative analyses. Figure 3 in the manufacturer's submission (MS) shows a flow diagram of the numbers of studies included and excluded at each stage of the review process (see the "Availability of Companion Documents" field).

Cost-effectiveness

- Nine cost-effectiveness studies met the inclusion criteria for the systematic review but only one was deemed relevant by the manufacturer for discussion. In addition, the manufacturer identified one relevant National Institute for Health and Care Excellence (NICE) single technology appraisal, "Vemurafenib for the treatment of locally advanced or metastatic BRAF v600 mutation-positive malignant melanoma (NICE technology appraisal 269)."
- The manufacturer submitted an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Data Extraction

Details of the data extraction strategy are reported in the manufacturer's submission (MS) (see the "Availability of Companion Documents" field). Data from the included studies were appropriately extracted in parallel by two independent reviewers with any differences considered and

reconciled by a third reviewer. Where more than one identified publication described a single trial, data were appropriately compiled into a single entry in the data extraction table to avoid the double counting of patients. The types of data extracted appear to be comprehensive.

Quality Assessment

A descriptive critical appraisal of all the included studies was conducted using comprehensive assessment criteria based on the recommendations in the NICE Single Technology Assessment (STA) guidelines.

Evidence Synthesis

All trials identified by the systematic review had different interventions and comparators and therefore it was not possible to conduct a meta-analysis. Findings were appropriately presented narratively. In addition, to compare interventions to comparators specified in the NICE scope, the manufacturer undertook an indirect treatment comparison (ITC).

Refer to section 4 in the ERG report for additional information on clinical effectiveness.

Cost-effectiveness

Overview of Manufacturer's Economic Modelling

Description of Manufacturer's Economic Model

A schematic of the manufacturer's model is provided in the MS and reproduced in Figure 2 in the ERG report. It comprises three health states described as progression-free, post progression and death. All patients enter the model in the 'progression-free' health state and are at risk of disease progression or death over time. Patients who progress are assumed to discontinue therapy, move to the 'Post progression' health state and stay in that health state until death. The model has been developed in Microsoft Excel and employs a 1-week cycle length.

Perspective, Time Horizon and Discounting

The manufacturer states that the economic appraisal is undertaken from the perspective of the National Health Service (NHS). Outcomes are expressed in terms of quality adjusted life years (QALYs) and life-years gained. The time horizon is set at 30 years and, in line with the NICE Methods Guide to Technology Appraisal, both costs and outcomes are discounted at 3.5%.

Refer to sections 5 and 6 in the ERG report for more information on cost-effectiveness assessment.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee did not consider the cost-effectiveness of dabrafenib compared with dacarbazine, having noted that dacarbazine was not an appropriate comparator as it was no longer used in clinical practice. It restricted its cost-effectiveness discussion to the comparison with vemurafenib.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee noted the Evidence Review Group's (ERG's) concerns regarding the structure of the model; in particular, the way the company modelled the clinical effectiveness estimates using a 3-stage approach, resulting in survival curves that did not appear clinically plausible. The Committee also noted the ERG's concerns with the company's indirect comparison and noted that the ERG had not carried out exploratory analyses of the clinical or cost effectiveness of dabrafenib compared with vemurafenib.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Treatment-specific EuroQoL EQ-5D utility data for pre-progression and post-progression, derived directly from BREAK-3, were used in the model for dabrafenib and dacarbazine. In the absence of comparable EQ-5D utility data for vemurafenib, the company assumed that the vemurafenib utility values would be the same as those for dabrafenib.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

Not applicable

What Are the Key Drivers of Cost-effectiveness?

The company conducted a series of deterministic sensitivity analyses. For the comparison of dabrafenib with dacarbazine, overall survival was the key driver of the cost-effectiveness results.

The key driver of the cost-effectiveness result for the comparison of dabrafenib with vemurafenib was the progression-free survival assumption.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-effectiveness Ratio [ICER])

The Committee noted that the company's base case ICER was £11,000 per quality-adjusted life year (QALY) gained for dabrafenib compared

with vemurafenib, but was much lower than this if a class effect was assumed for dabrafenib and vemurafenib. In the absence of any further numerical analysis by the ERG, the Committee could not give an estimate of the most plausible ICER for the comparison of dabrafenib with vemurafenib.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the company that manufactures dabrafenib and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from an international, multi-centre, randomised, open-label, active-controlled trial. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma

Potential Harms

- The summary of product characteristics lists the following very common adverse reactions for dabrafenib: papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills and asthenia.
- The data from the December 2012 analysis of the BREAK-3 trial showed that the most commonly reported grade 3 adverse events with dabrafenib were pyrexia, back pain, squamous cell carcinoma and hyperglycaemia; whereas neutropenia, decreased appetite and leukopenia had a higher incidence in the dacarbazine arm.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has unresectable or metastatic BRAF V600 mutation-positive melanoma and the doctor responsible for their care thinks that dabrafenib is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the company have agreed that dabrafenib will be available to the NHS with a patient access scheme that makes dabrafenib available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the manufacturer's customer contact centre on 0800 221 441.
- NICE has developed a costing statement explaining the resource impact of this guidance (see also the "Availability of Companion Documents" field).

Implementation Tools

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Technology appraisal guidance; no. 321).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Oct

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site.

Availability of Companion Documents

The following are available:

- Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 1 p. (Technology appraisal guidance; no. 321). Available from the National Institute for Health and Care Excellence (NICE) Web site.
- Fleeman N, Bagust A, Beale S, Boland A, Dickson R, Dwan K, Richardson M, Dundar Y, Davis H, Banks L. Dabrafenib for the treatment of unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma [ID605]: a single technology appraisal. Liverpool (UK): Liverpool Reviews and Implementation Group (LRiG); 2014. 97 p. Available from the NICE Web site.
- Melanoma (unresectable/metastatic BRAFV600 mutation-positive) - dabrafenib. Single technology appraisal (STA). Manufacturer's submission. GlaxoSmithKline UK; 2014 Apr. 210 p. Available from the NICE Web site.

Patient Resources

The following is available:

- Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 3 p. (Technology appraisal guidance; no. 321). Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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